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## EVALUATION OF TESTS USED IN THE DIAGNOSIS OF PHEOCHROMOCYTOMA\*

### PART I

The increasing number of reports of pheochromocytoma has presented an opportunity to assess the value of pharmacological tests used as an aid in the diagnosis of this condition. The purpose of this paper and a subsequent one is to reevaluate these tests in cases of pheochromocytoma which have been reported in the American and English literature during the last 4-5 years and in which the diagnosis has been proved at autopsy or operation. Data concerning the use of these agents in hypertensive patients without pheochromocytoma and in normotensive patients have been included. Two additional procedures, the cold pressor tests and measurements of epinephrine and nor-epinephrine in the blood and urine, which are claimed to be helpful in the diagnosis, will also be commented upon. Older methods used to make a diagnosis of pheochromocytoma, such as change in posture, abdominal massage, and perirenal air insufflation, are much less reliable than the pharmacological tests.

The clinical manifestations of pheochromocytoma have been fully described.<sup>1,2</sup> Features which commonly distinguish this condition from hypertension due to other causes include vasomotor instability, elevated body temperature, excessive sweating, increased blood sugar levels, elevation of the basal metabolic rate, and paroxysmal attacks during which the blood pressure is elevated. It is well established, however, that pheochromocytoma may be associated with a persistent elevation of blood pressure and that clinically it can simulate essential hypertension. These facts provide strong support for the view that the pheochromocytoma tests should be done in most patients with hypertension.<sup>3</sup>

The pharmacological tests are divided into two categories: one consisting of those drugs which induce a pressor response in pheochromocytoma patients, such as histamine, mecholyl, and tetraethylammonium chloride; the other consisting of

those drugs which induce a depressor response in patients with pheochromocytoma, such as benzo-dioxane, regitine, and dibenamine. This communication will be confined to a presentation of the data on the first group of drugs and on the cold pressor test. The evaluation of drugs causing a depressor response and the tests which measure the amount of pressor substances in the blood and urine will be presented in the May, 1954 issue of *Modern Concepts of Cardiovascular Disease*.<sup>4</sup>

#### Cold Pressor Test

Contradictory views have been expressed regarding the incidence of hyper-reactors and normal-reactors to the cold pressor stimulus in patients with pheochromocytoma. According to Hines and Brown,<sup>5</sup> who described the test in 1932, persons showing a response greater than 20/15 on immersing the hand into ice water were defined as hyper-reactors. Those showing a response at or less than 20/15 were termed normal reactors.

We have reviewed the 13 cases of proven pheochromocytoma reported since 1949, in which the cold pressor test had been done. To this number we have added the nine pheochromocytoma patients in Smithwick's series<sup>1</sup> as well as the pheochromocytoma patients with reported cold pressor tests reviewed by him prior to 1949, making a total of 33 patients. Of this number, 15 or 45 per cent were hyper-reactors. In a series of 100 patients with essential hypertension reported by Smithwick, 22 per cent were normal-reactors to the cold pressor test. It is apparent, therefore, that given a patient with hypertension, the cold pressor test gives no decisive information as to the presence or absence of pheochromocytoma.

#### Histamine Test

The histamine test for the diagnosis of pheochromocytoma was proposed and standardized by Roth and Kvale<sup>6</sup> in 1945. They found that the rapid intravenous injection of 0.025-0.05 mg. of histamine base in patients with proved pheochro-

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mocytoma produced a pressor response in excess of the elevation of blood pressure noted in the cold pressor test. The mechanism of action of histamine in causing the pressor response has not been fully elucidated. Cumulative evidence obtained by Dale,<sup>7</sup> Burn,<sup>8</sup> Feldberg,<sup>9</sup> and others support the view that histamine can cause epinephrine liberation by stimulation of the adrenal medulla directly and not reflexly by an initial fall in blood pressure.

#### *Test Procedure.*

Because of the rather marked pressor effect which is expected in the presence of pheochromocytoma from histamine administration, the test is to be recommended for use in those patients in whom the resting blood pressure level does not exceed 150 mm. for the systolic and 110 mm. for the diastolic pressure. A cold pressor test should be done in conjunction with the histamine test for purposes of comparing the pressor responses from the two procedures. The technique of the cold pressor test has been described.<sup>5</sup> After the patient has been lying in a quiet room for 15 minutes or until the blood pressure has become stabilized, the blood pressure is recorded at 30-second or 1-minute intervals for a period of 5 minutes. An intravenous infusion of 5 per cent glucose in water is then started and repeated determinations of the blood pressure are made until the pressor effect of the needle puncture subsides. The histamine in a dosage of 0.025-0.05 mg. is then rapidly injected through a 3-way stopcock attached to the intravenous infusion and the blood pressure is recorded every 30 seconds for the next four minutes and at 1-minute intervals for the remaining 15 minutes.

The criteria for a positive result is a pressor response in which there is a systolic blood pressure rise of 60 mm. or above and a diastolic rise of 30 mm. or above, occurring promptly within 1 to 4 minutes after the injection and with the blood pressure returning to the pre-injection level in 5 to 15 minutes or occasionally longer. The positive histamine response should exceed the cold pressor response.

Since 1949 we have found 27 patients with pheochromocytoma in whose reports there were adequate data to evaluate the histamine test. In 21 of these cases, the test was unequivocally positive with significant pressor responses. In 5 cases,<sup>2, 10, 11, 12, 13</sup> the histamine test gave a false negative response and in one patient,<sup>2</sup> the result was equivocal.

In the 21 unequivocally positive tests the range of the maximum pressor response was 60 to more than 200 mm. systolic and 30 to 110 mm. diastolic above the control levels. The average systolic rise was 111 mm. and the average diastolic rise, 60 mm. The maximum pressor response occurred promptly within 1 to 4 minutes after histamine injection. The time taken for the blood pressure to return to the control resting value was specified in only 11 of these 21 cases. It was from 5

to 15 minutes in 9 cases, 26 minutes in one case, and two hours in another case. Results of the cold pressor tests were reported in only 10 of the 21 cases with a positive histamine test. In response to the cold pressor stimulus the average systolic rise was 37 mm., and the average diastolic rise, 28 mm. In each of these 10 cases the histamine pressor response was greater than the cold pressor response.

The false negative tests deserve special comment in as much as failure to adhere to the standard conditions of the test may have been responsible for a negative result in 3 of the 5 patients.<sup>2, 10, 11</sup> In a 24-year-old female patient reported by Bartels<sup>2</sup> in whom a pheochromocytoma of the left adrenal gland was removed, sedation and anesthesia consisting of pantopon, gr. 1/6, scopolamine, gr. 1/150, and avertin 90 mg. given rectally were used to obtain a stable blood pressure just prior to the test. This circumstance plus the fact that the histamine was injected at a slow rate may have been responsible for the lack of a pressor response. In two other patients,<sup>10, 11</sup> the blood pressure levels were very high just prior to the histamine administration. In one of these cases, reported by Shapiro,<sup>10</sup> the resting control blood pressure was 210/145 and, following the rapid intravenous injection of histamine 0.0005 mg./kg., the maximum pressure response was only 18/20. We raise the question whether the negative histamine response in these two patients may have been attributable to the failure of the adrenal tumor to increase further its pressor substances in response to the histamine stimulation. This would not be generally the case, however, since there were 6 patients<sup>14, 15, 16, 17, 3</sup> among the 21 patients with a positive histamine test who had high resting control diastolic blood pressures of 110 mm. or more.

No proven false positive histamine test was encountered in our review of the literature except in the patient mentioned by Calkins et al<sup>13</sup> in whom a pressure rise of 100 mm. systolic and 50 mm. diastolic was noted after histamine injection and in whom no tumor was found at operation. The details of the test are not stated and the possibility still remains that a tumor was present. Recently we have studied a patient who had an 80 mm. rise in systolic pressure and a 35 mm. rise in diastolic pressure following a histamine injection. A thorough laparotomy in this patient did not reveal the presence of pheochromocytoma. This case then would represent a second instance in which a false positive histamine test is known to us. Roth and Kvale<sup>18</sup> performed the test in 9 normal subjects, in 22 patients who were hyper-reactors to the cold pressor test, and in 16 patients with well-established hypertension but presumably without pheochromocytoma. In all of these cases the histamine pressor response was less than the cold pressor response. Strong evidence in favor of the reliability of the histamine test exists in the fact that the pressor response to histamine was not found after removal

of the tumor in the 8 patients in whom this test was done post-operatively.

In this series of 27 cases with adequate data regarding response to the histamine test, an alarming pressor response with the systolic blood pressure reaching 280 mm. or more occurred in 6 cases. In 5 of these patients the resting control systolic pressure was 150 or above and the resting control diastolic 110 or above. An alarming pressure response occurred in one patient<sup>19</sup> whose resting systolic pressure was 100 mm. and resting diastolic level was 70 mm. No cerebral or coronary vascular accidents were reported to have resulted from the use of the test. It is good practice to have benzodioxane to administer intravenously (15 to 20 mgm.) in the event of a marked pressor reaction.

### Mecholyl Test

Mecholyl was used by Guarneri and Evans<sup>20</sup> as a diagnostic procedure in a case of pheochromocytoma in 1948. They found that the subcutaneous injection of 25 mg. of the drug produced a marked pressor response. Recently these authors suggested a reduction in the dosage to 10 mg.

We have found six cases of proven pheochromocytoma in which mecholyl was used as a diagnostic procedure. There were two false negative tests,<sup>10,21</sup> two positive tests,<sup>2,22</sup> and two tests with equivocal results.<sup>2</sup> With the data at hand the value of the test cannot be adequately assessed.

### Tetraethylammonium Chloride (Etamon) Test

LaDue, Murison and Pack<sup>23</sup> suggested the intravenous use of tetraethylammonium chloride as a diagnostic test for pheochromocytoma and described the method to be employed in 1947. A positive response consists of an immediate elevation of blood pressure which persists for about 15 minutes following the injection of 100-400 mg. of the drug intravenously.

We have found ten cases of proven pheochromocytoma with an adequately reported Etamon test. There were three positive tests,<sup>24,10,25</sup> six false negative results,<sup>26,2,27,28,29,30</sup> and in two patients<sup>2,31</sup> the test was uninterpretable. This test is therefore not to be recommended as an aid in the diagnosis of pheochromocytoma.

### Summary

1. *Cold Pressor Test.* This test in itself does not contribute to the diagnosis of pheochromocytoma. It is, nevertheless, of assistance in assessing the results of the histamine or mecholyl test.

2. *Histamine Test.* This test is well standardized and is to be used in suspected cases of pheochromocytoma in which the resting control blood pressure preferably does not exceed 150 mm. systolic and 110 mm. diastolic. No sedatives or narcotics of any kind should be used for 24 hours prior to the test. Although occasional un-

explained false negative tests will occur despite all precautions, the test is quite reliable for suspected cases of pheochromocytoma with paroxysmal attacks of hypertension. That removal of the tumor abolishes the pressor response to the histamine test is good evidence in favor of its high degree of specificity.

3. *Mecholyl Test.* More data should probably be accumulated on the use of the mecholyl test. From the results available, this test appears to be less reliable than the histamine test.

4. *Tetraethylammonium Chloride (Etamon) Test.* Because of the high incidence of false negative tests, the use of tetraethylammonium is to be discouraged as a diagnostic test for pheochromocytoma.

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The opinions and conclusions expressed herein are those of the author and do not necessarily represent the official views of the Scientific Council of the American Heart Association.

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